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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/667,281	09/17/2003	John David Allard	R0066C-DIV	8643

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EXAMINER

MOORE, WILLIAM W

ART UNIT	PAPER NUMBER
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1656

DATE MAILED: 09/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/667,281

Applicant(s)

ALLARD ET AL.

Examiner

William W. Moore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 33-35 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 33-35 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 20030917.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____.

DETAILED ACTION*Priority*

Applicant's claim to priority of the 10 May 1999 filing date of a parent US provisional application serial No. 60/133,343, stated in the Amendment to the first page of the specification filed 17 September 2003, is hereby acknowledged. In responding to this communication, Applicant is invited to further amend page 1 of the specification to revise the data for the instant application by including the status of the intervening US utility application serial No. 09/568,559, in the chain of priority.

Information Disclosure Statement

Applicant's Information Disclosure Statement [IDS] filed with the application on 18 July 2003 is hereby acknowledged.

Preliminary Amendment

Applicant's Preliminary Amendment filed with the application on 18 July 2003 has been entered, amending the first page of the specification, canceling claims 1-32 and adding the new claims 33-35 which are examined herein.

Claim Objections

Claim 33 is objected to because of the following informalities: Claim 33 lacks an article, such as the indefinite article "an", at the beginning of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-35 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

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reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the preparation of the subject matters of the divergent aggrecanases and fragmentary aggrecanases of claims 33-35. While the specification identifies a particular, integral, aggrecanase having the amino acid sequence set forth in SEQ ID NO:2, the suggestion at page 5 of the specification that proteins having amino acid sequences from 50% to 70% identical to SEQ ID NO:2 are included in a claimed invention is not supported by a disclosure of a significant number of alternative species adequate to demonstrate possession of such broad genera of divergent aggrecanases. Similarly, the suggestions at pages 6 and 7 of the specification that fragments of the of the amino acid sequence set forth in SEQ ID NO:2 are included in a claimed invention is not supported by a disclosure of the preparation of any particular fragments or by a description of where the boundaries of any fragments should occur within SEQ ID NO:2, and there is no teaching of the boundaries required for a fragment of SEQ ID NO:2 that will retain the proteolytic activity of an aggrecanase. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification furnishes no relevant identifying characteristics either of divergent aggrecanases or aggrecanase fragments, nor does it provide any characteristics permitting a correlation between the undisclosed divergent aggrecanases, or aggrecanase fragments, and the disclosed amino acid sequence of SEQ ID NO:2. Nothing demonstrates that, at the time the specification was filed, Applicant was "able to envision" enough of the structure of an undisclosed, generic, aggrecanase, or fragment, to provide the public with identifying "characteristics [that] sufficiently distinguish it . . . from other materials". *Fiers*, 25 USPQ2d at 1604 (citing *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016,

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1021 (Fed. Cir. 1991). The specification's treatment of the claimed subject matter is entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the structure, or other properties, of the generic aggrecanases of claims 33 and 34, or the boundaries of an aggrecanase fragment of claim 35.

Claims 33-35 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the preparation of an aggrecanase comprising the amino acid sequence set forth in SEQ ID NO:2, does not reasonably provide enablement for the preparation of divergent aggrecanases or aggrecanase fragments that retain proteolytic activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 33 and 34 contemplate arbitrary assignment of amino acid substitutions, additions or deletions within the aggrecanase amino acid sequence of SEQ ID NO:2 that, where the term "substantially" in claim 34 has no definite dimension, thus reach modification of at least 30% of the amino acid positions in SEQ ID NO:2, i.e., as many as 285 amino acids in the 949-amino acid sequence of SEQ ID NO:2. Yet the specification cannot support even a few amino acid alterations within the sequence of SEQ ID NO:2, which are amino acid insertions, deletions, or substitutions anywhere, in any combination or any pattern, within SEQ ID NO:2. Similarly, the specification fails to teach the boundaries of a fragment of SEQ ID NO:2 that can retain the proteolytic activity of an aggrecanase. Indeed, neither the prior art made of record herewith nor Applicant's specification can identify, taken together, as many as ten amino acids in the amino sequence of SEQ ID NO:2 that might be altered, nor teach the nature of an alteration that may be made, which permits a resulting polypeptide to function as an aggrecanase. Mere sequence perturbation cannot enable the design and preparation of nucleotide sequences encoding a myriad of divergent aggrecanases and provide the public with an aggrecanase that retains its native function.

It is well settled that 35 U.S.C. § 112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed

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without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (discussing eight factors relevant to analysis of enablement). Applying the analysis factors discussed in *Wands* to Applicant's disclosure, it is apparent that:

- a) the specification lacks adequate, specific, guidance for altering the amino acid sequence of the aggrecanase of SEQ ID NO:2 to the extent permitted by claims 33-35 construed in light of the suggestions in the specification,
- b) the specification lacks working examples wherein the aggrecanase of SEQ ID NO:2 is altered to the extent recited in the claims,
- c) in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,
- d) unpredictability exists in the art where no members of the class of proteases represented by amino acid sequence of SEQ ID NO:2, have had even a few amino acids specifically identified for concurrent modification.

Thus the scope of subject matters embraced by claims 33-35 construed according to the suggestions of the specification are unsupported by the present specification even if taken in combination with teachings available in the prior art.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34 and 35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 is indefinite because it depends from the canceled claim 1, and is further indefinite in its recitation of "substantially identical" because the term "substantially" has no particular dimension and the artisan and the public seeking to determine the metes and bounds of the intended subject matter cannot know the extent of non-identity that something which is "substantially identical" might possess. Claim 34 as additionally indefinite in reciting "amino acid sequence identi[ty] to . . . SEQ ID NO:1, which is a nucleic acid sequence. The appropriate reference would be to SEQ ID NO:2, which is an amino acid sequence. Claim 35 is included in this rejection because it fails to resolve the ambiguities of claim 34 from which it depends and, indeed, compounds the

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ambiguity where the public and the artisan cannot know where a fragment of something already non-identical becomes less identical because it is fragmentary yet remains "substantially identical". Adopting the recitations of the amendments to claims 34 and 35 proposed at the close of the following rejections of claims herein over the prior art would overcome this rejection of both claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 33-35 are rejected under 35 U.S.C. § 102(a) as being anticipated by Moore et al., WO 98/56804, made of record herewith.

Moore et al. disclose an isolated human metalloproteinase in their SEQ ID NO:174, encoded by their Gene 64, that is inherently an aggrecanase because it differs from SEQ ID NO:2 herein by an N-terminal extension of eighteen amino acids and seven relative amino acid substitutions at positions 22, 141, 209, 275, 279, 529, and 532 of SEQ ID NO:2 herein, thus is "substantially identical" to SEQ ID NO:2 herein. Moore et al. also disclose fragments of the metalloproteinase of their SEQ ID NO:174 at page 59 of WO 99/37660, meeting all limitations of claims 33-35 herein.

Claims 33-35 are rejected under 35 U.S.C. §§ 102(a) and 102(e) as being anticipated by Holtzman et al., WO 99/07850 and US 6,416,974, both made of record herewith.

Holtzman et al. disclose an isolated human Tango-71 metalloproteinase in their SEQ ID NO:2 that is inherently an aggrecanase because it differs from SEQ ID NO:2

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herein only by an N-terminal extension of eighteen amino acids and two relative amino acid substitutions at positions 209 and 532 of SEQ ID NO:2 herein, thus is "substantially identical" to SEQ ID NO:2 herein. Holtzman et al. also disclose fragments of their SEQ ID NO:2 at, e.g., page 7, lines 15-27 of WO 99/07850, where the fragments are separate domains or epitope regions of the metalloproteinase, meeting all limitations of claims 33-35 herein.

Claims 33-35 are rejected under 35 U.S.C. §§ 102(b) and 102(e) as being anticipated by Jonak et al., EP 874050, US 2003/0166056, and US 2004/0175794, all made of record herewith.

Jonak et al. disclose an isolated human "ITGL-TSP" polypeptide in their SEQ ID NO:2 that is inherently an aggrecanase because it differs from SEQ ID NO:2 herein only by an N-terminal extension of eighteen amino acids and two relative amino acid substitutions at positions 209 and 532 of SEQ ID NO:2 herein, thus is "substantially identical" to SEQ ID NO:2 herein. Jonak et al. also disclose various fragments of their ITGL-TSP's SEQ ID NO:2 at, e.g., the close of page 4 of their EP 874050, meeting all limitations of claims 33-35 herein.

Claims 33-35 are rejected under 35 U.S.C. § 102(e) as being anticipated by Iruela-Arispe et al., US2003/0092900, made of record herewith.

Iruela-Arispe et al. disclose an isolated human Meth-1 metalloproteinase in SEQ ID NO:2 that is inherently an aggrecanase because it differs from SEQ ID NO:2 herein only by two relative amino acid substitutions at positions 209 and 532 of SEQ ID NO:2 herein, thus is "substantially identical" to SEQ ID NO:2 herein. Iruela-Arispe et al. also disclose fragments of their SEQ ID NO:2, see, e.g., pages 55-64 and 66-92 of their WO 99/37660 that shares the same US priority patent applications and the identical SEQ ID NO:2 and is also made of record herewith, meeting all limitations of claims 33-35 herein.

Allowable Subject Matter

Because the alterations of prior art aggrecanase amino acid sequences that would result in the specific amino acid sequence set forth in SEQ ID NO:2 herein are not

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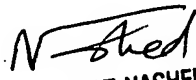
disclosed or taught in the prior art of record, the rejections above under the several paragraphs of 35 U.S.C. § 102, as well as the rejections above under U.S.C. § 112, first and second paragraphs, may be overcome by canceling claim 33 and amending claim 34 to describe, "[A]n isolated aggrecanase comprising the amino acid sequence set forth in SEQ ID NO:2", and also amending claim 35 to make it an independent claim that describes "[A]n isolated aggrecanase that consists of the amino acid sequence set forth in SEQ ID NO:2". These amendments were stated on 14 September 2005 to Applicant's counsel in the form of an examiner's amendment to facilitate allowance of claims 34 and 35 herein but were not accepted.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933 and whose FAX number is 571.273.0933. The examiner can normally be reached Monday through Friday between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisory Primary Examiner, Dr. Kathleen Kerr, can be reached at 571.272.0931. The official FAX number for all communications for the organization where this application or proceeding is assigned is 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
15 September 2005


NASHAAT T. NASHED PHD.
PRIMARY EXAMINER